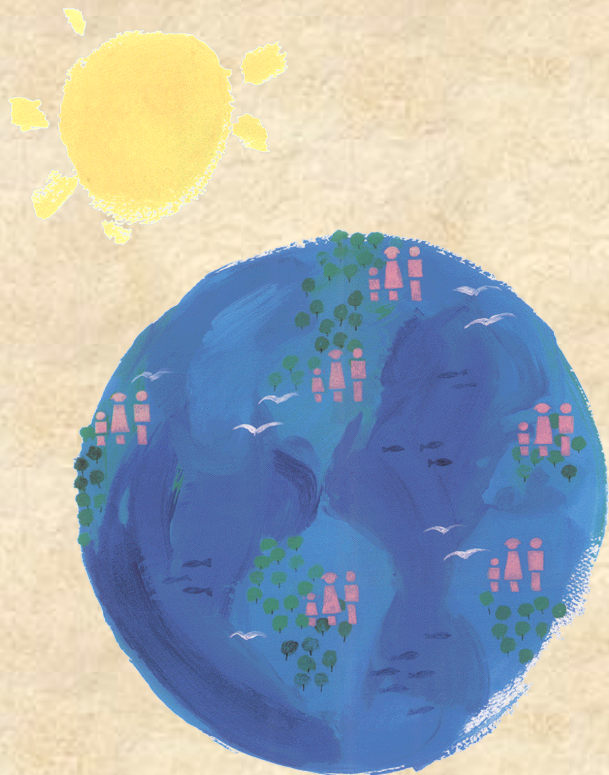


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National Toxicology Program Interagency
Center for the Evaluation Of Alternative
Toxicological Methods

ICCVAM

Interagency Coordinating Committee
on the Validation of Alternative
Methods

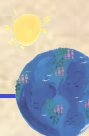


Proposed Reference Substances: BRD Summary

Expert Panel Meeting
January 11-12, 2005
Bethesda, Maryland

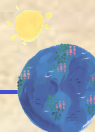


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Reference Substances for Validation Studies

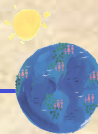
- According to the ICCVAM Submission Guidelines (ICCVAM, 2003), to the extent possible, reference substances should:
 - Be representative of the range of responses for which the proposed test method is expected to cover (i.e., nonirritants and mild, moderate, or severe eye irritants)
 - Represent the classes of chemicals for which the proposed test method is expected to be used.
 - Have produced high quality results (i.e., produced in a GLP compliant study) in the reference test method and/or the species of interest
 - Have well-defined chemical composition
 - Be readily available
 - Not be associated with excessive hazard or prohibitive disposal costs



Proposed Reference Substances (I)

- Coverage of the Range of Anticipated Responses:

Classification (GHS)	Total Database	Commercially Available	Recommended for Validation
Category 1	123	48	48
Category 2A	24	11	11
Category 2B	68	27	15
Nonirritant	277	111	15
Total	492	197	89

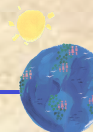


Proposed Reference Substances (II)

- Coverage of the range of anticipated responses within Category 1 substances (commercially available):

Subcategory	Criteria	Number
4	CO = 4 at any time (1/3 animals)	24
3	Positive response based on mean for first 3 days (2/3 animals with CO \geq 3 or IR \geq 1.5) and a persistent (\geq 21 days) lesion	2
2	Positive response based on mean for first 3 days (2/3 animals), not persistent	4
1	Positive response based on a persistent lesion and not severity (1/3 animals)	18
	Total	48

CO = Corneal Opacity; IR = Iritis



Proposed Reference Substances (III)

- *In vivo* data source

GHS Category	CTFA	ECETOC	EPA-TSCA	FDA	NIHS	Total
Category 1	7	26	5	2	8	48
Category 2A	0	10	1	0	0	11
Category 2B	1	13	1	0	0	15
Nonirritant	2	12	0	1	0	15
Total	10	61	7	3	8	89

CTFA: Cosmetic, Toiletry, and Fragrance Association

ECETOC: European Centre for Ecotoxicology and Toxicology of Chemicals

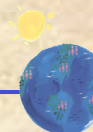
EPA-TSCA: U.S. Environmental Protection Agency – Toxic Substances Control Act

FDA: U.S. Food and Drug Administration

NIHS: National Institute of Health Sciences - Japan

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Chemical Classes Represented Among the Reference List

Class	Total	Cat 1	Cat 2A	Cat 2B	NI
Surfactant	13	8	2	1	2
Alcohol	13	3	3	6	1
Surfactant Formulation	9	7	0	1	1
Acid	7	7	0	0	0
Miscellaneous	5	4	0	0	1
Sulfur-Containing	4	2	0	1	1
Inorganic	4	2	0	1	1
Heterocycle	4	3	0	0	1
Organic Salt	4	3	0	1	0
Alcoholic Formulation	3	2	0	0	1
Hydrocarbon	3	0	0	1	2
Ketone	3	0	1	1	1
Acetate	2	0	1	1	0
Acrylate	2	1	0	0	1
Nitrile	2	1	0	1	0
Silane/Siloxane	2	2	0	0	0
Other*	9	3	4	0	2
Total	89	48	11	15	15

*Other Classes Include (n = 1): Acyl halide, Aldehyde, Alkali, Amine, Isocyanate, Methacrylate, Oil/ Water formulation, Organophosphate, Polychlorinated

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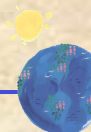
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Chemical Classes Represented Among Category 1 Subcategories

Class/Cat 1 Subcategory	Total	4	3	2	1
Surfactant	8	3	0	2	3
Anionic Surfactant	1	0	0	0	1
Cationic Surfactant	6	3	0	2	1
Nonionic Surfactant	1	0	0	0	1
Acid	7	4	0	1	2
Surfactant Formulation	7	0	0	0	7
Miscellaneous	4	2	2	0	0
Alcohol	3	1	0	1	1
Heterocycle	3	3	0	0	0
Organic Salt	3	3	0	0	0
Alcoholic Formulation	2	0	0	0	2
Inorganic	2	1	0	0	1
Silane/Siloxane	2	1	0	0	1
Sulfur-Containing	2	1	0	0	1
Other*	5	5	0	0	0
Total	48	24	2	4	18

*Other Classes Include (n = 1): Acrylate, Alkali, Amine, Isocyanate, Nitrile



Product Classes Represented Among the Reference List

Class	Total	Cat 1	Cat 2A	Cat 2B	NI
Solvent	12	1	3	7	1
Industrial Chemical	10	6	2	1	1
Unclassified	10	5	0	1	4
Disinfectant/Germicide	8	7	1	0	0
Soaps/Surfactants	7	6	0	0	1
Cosmetic	6	4	1	0	1
Chemical Intermediate	5	2	1	1	1
Herbicide/Pesticide	5	3	1	1	0
Shampoos	5	4	0	1	0
Detergent	4	0	1	1	2
Pesticide/Pharmaceutical Intermediate	4	1	0	2	1
Anti-fungal/Anti-infective	3	2	1	0	0
Pharmaceutical	3	2	0	0	1
Cleaner	2	2	0	0	0
Lotions/Sunscreens	2	1	0	0	1
Other*	3	2	0	0	1
Total	89	48	11	15	15

*Other Classes Include (n = 1): Acyl halide, Aldehyde, Alkali, Amine, Isocyanate, Methacrylate, Oil/ Water formulation, Organophosphate, Polychlorinated

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Product Classes Represented Among Category 1 Substances

Class/Cat 1 Subcategory	Total	4	3	2	1
Disinfectant/Germicide	7	4	0	2	1
Industrial Chemical	6	4	0	0	2
Soaps/Surfactants	6	0	0	0	6
Unclassified	5	5	0	0	0
Cosmetic	4	3	0	0	1
Shampoos	4	0	0	0	4
Herbicide/Pesticide	3	3	0	0	0
Anti-fungal/Anti-infective	2	1	1	0	0
Chemical Intermediate	2	0	0	1	1
Cleaner	2	1	0	0	1
Pharmaceutical	2	0	1	0	1
Other*	5	3	0	1	1
Total	48	24	2	4	18

*Other Classes Include (n = 1): Acrylate, Alkali, Amine, Isocyanate, Nitrile

